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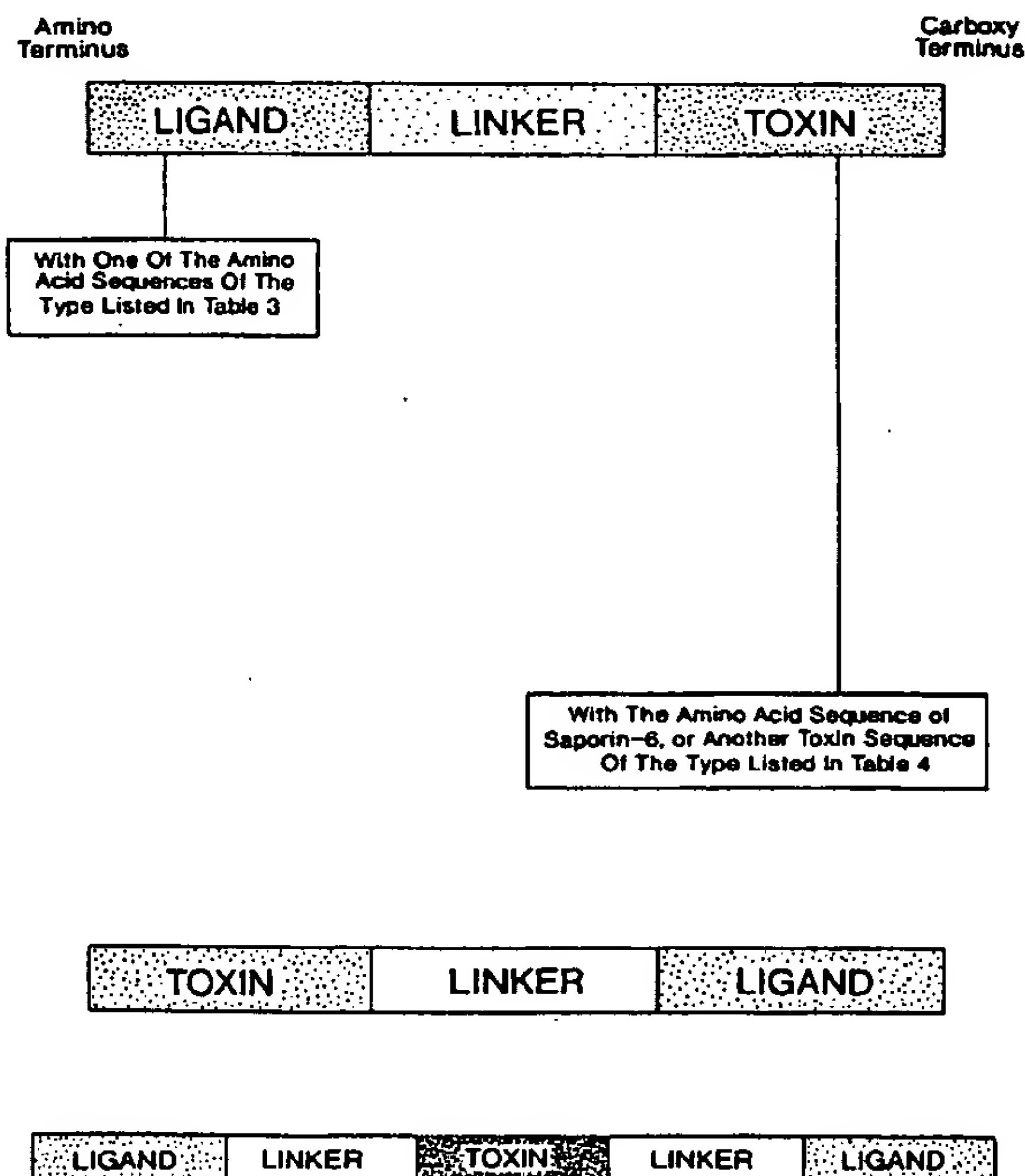
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : <b>A61K 47/48, 48/00, C12N 15/19, 15/62, 15/29, 15/31, C07K 14/52, 19/00, 14/415</b>		<b>A3</b>	(11) International Publication Number: <b>WO 00/04926</b>
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(21) International Application Number: <b>PCT/CA99/00659</b>		(74) Agents: MORROW, Joy, D. et al.; Smart & Biggar, 900-55 Metcalfe Street, Station D., P.O. Box 2999, Ottawa, Ontario K1P 5Y6 (CA).	
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(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/120,523 (CIP) Filed on 22 July 1998 (22.07.98)		Published With international search report.	
(71) Applicant (for all designated States except US): OSPREY PHARMACEUTICALS LIMITED [CA/CA]; 3400 Petro-Canada Centre, 150-6th Avenue SW, Calgary, Alberta T2P 3Y7 (CA).		(88) Date of publication of the international search report: 2 November 2000 (02.11.00)	
(72) Inventors; and (75) Inventors/Applicants (for US only): MCDONALD, John, R. [GB/CA]; 60 Governor Drive SW, Calgary, Alberta T3E 4Y9 (CA). COGGINS, Philip, J. [CA/CA]; 4211, 5A Street SW, Calgary, Alberta T2S 2G8 (CA).			

(54) Title: METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS

## (57) Abstract

Conjugates containing as a ligand a chemokine receptor targeting agents, such as chemokines, and a targeted agent, such as a toxin are provided. These conjugates are used to treat inflammatory responses associated with activation, proliferation and migration of immune effector cells, including leukocyte cell types, neutrophils, macrophages, and eosinophils. The conjugates provided herein are used to lessen or inhibit these processes to prevent or at least lessen the resulting secondary effects. In particular, the conjugates are used to target toxins to receptors on secondary tissue damage-promoting cells. The ligand moiety can be selected to deliver the cell toxin to such secondary tissue damage-promoting cells as mononuclear phagocytes, leukocytes, natural killer cells, dendritic cells, and T and B lymphocytes, thereby suppressing the proliferation, migration, or physiological activity of such cells. Among preferred conjugates are fusion proteins having a chemokine, or a biologically active fragment thereof, as the ligand moiety linked to a cell toxin via a peptide linker of from 2 to about 60 amino acid residues.



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# INTERNATIONAL SEARCH REPORT

International Application No  
PC1/CA 99/00659

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/48 A61K48/00 C12N15/19 C12N15/62 C12N15/29  
C12N15/31 C07K14/52 C07K19/00 C07K14/415

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	P ROBY ET AL: "Melanoma-specific cytotoxicity of a human MGSA/GROalpha C-terminal peptide conjugated to daunorubicin" ONCOLOGY REPORTS, vol. 3, 1996, pages 175-179, XP000881561 abstract "Cytotoxicity..Etc" on pages 177 to 178 discussion ---	1-43,65, 73-75
X	WO 95 12414 A (REPLIGEN CORP) 11 May 1995 (1995-05-11) example 26 claims 16-22 page 9, line 31 -page 10, line 9 --- -/--	1-47,65, 73-75,79



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

30 June 2000

Date of mailing of the international search report

14.08.00

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European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCI/CA 99/00659

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 07535 A (LYLE LEON R ;UNIV MICHIGAN (US); KUNKEL STEVEN L (US); MALLINCKRODT) 14 April 1994 (1994-04-14) examples 1-8 ---	1-43,65, 73-75
X	D I SILBERT: "Glycosaminoglycans of bovine aorta endothelial cells: Identification and localization by use of a platelet factor 4-fluorescein probe" JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, vol. 38, no. 4, 1990, pages 589-593, XP000881557 abstract ---	1-43,65, 73-75
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X	US 5 326 559 A (MILLER D DOUGLAS) 5 July 1994 (1994-07-05)  column 4, line 37 - line 41 column 8, line 3 - line 17 column 11, line 67 - line 68 ---	50-64, 67-71, 76-78
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International Application No  
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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X	RALPH, P.: "Clinical and preclinical studies presented by the keystone symposium on arthritis" LYMPHOKINE AND CYTOKINE RESEARCH, vol. 12, no. 4, August 1993 (1993-08), pages 261-263, XP000891639 abstract page 262, column 1, line 29 - line 47 ---	50-64, 67-71, 76-78
X	STROM, TERRY B. ET AL: "Interleukin-2 receptor-directed therapies: Antibody- or cytokine-based targeting molecules" ANNU. REV. MED. (1993), 44, 343-53, XP000915772 page 347 -page 351 ---	50-64, 67-71, 76-78
X	NAGPAL, SUNIL ET AL: "New dermatological agents for the treatment of psoriasis" ANNU. REP. MED. CHEM. (1997), 32, 201-210, XP000915751 "Introduction" on page 201 and the "New targets" on page 207 to 208 with reference to "fusion proteins" ---	50-64, 67-71, 76-78
X	ROBERGE, FRANCOIS G. ET AL: "Selective immunosuppression of activated T cells with the chimeric toxin IL - 2 -PE40. Inhibition of experimental autoimmune uveoretinitis" J. IMMUNOL. (1989), 143(11), 3498-502, XP002028689 abstract ---	50-64, 67-71, 76-78
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US SHEMYAKIN, I. G. ET AL: "Construction and expression in Escherichia coli cells of the fusion protein diphtheria toxin -human interleukin 2" retrieved from STN Database accession no. 119:40509 XP002141203 abstract & MOL. BIOL. (MOSCOW) (1992), 26(5), 1088-98, ---	50-54
X	HUSAIN, SYED R. ET AL: "Complete regression of established human glioblastoma tumor xenograft by interleukin -4 toxin therapy" CANCER RES. (1998), 58(16), 3649-3653, XP000910254 abstract --- -/--	50-53,64

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MENEGHETTI, CAROLE M. ET AL: "Initial clinical experiences with an interleukin -2 fusion toxin (DAB486- IL - 2 )" TARGETED DIAGN. THER. (1992), 7(GENET. ENG. TOXINS), 395-401, XP000915730 "III the chimeric fusion protein..Etc" on pages 396 to 399 ---	50-53,64
X	US 5 084 556 A (BROWN EUGENE L) 28 January 1992 (1992-01-28) column 5, line 31 -column 5, line 42 ---	50-53,64
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 99/00659

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: Claims 1 to 49, 65, 66,  
72 to 75 and 79 (Claims 52 to 64 and 68 to 71,  
76 to 78 in part)

Conjugates per se comprising (a) a targeted agent and (b) a CHEMOKINE receptor targeting agent which when applied to a receptor bearing cell results in internalization of (a) the targeted agent; associated nucleic acid/cells/pharmaceutical compositions; methods and uses involving said conjugates

2. Claims: Claims 50, 51, 67 (Claims 52 to 64, 68 to 71,  
76 to 78 in part)

Treatment of INFLAMMATORY DISORDERS using a conjugate comprising a NON-CHEMOKINE CYTOKINE



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00659

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